Role of age-related alterations of the cerebral venous circulation in the pathogenesis of vascular cognitive impairment

Gabor A. Fulop MD[*,1,2,3], Stefano Tarantini PhD[*,1,2], Andriy Yabluchanskiy MD, PhD[1,2], Andrea Molnar, MD, PhD[3] Calin I. Prodan, MD[4,5], Tamas Kiss, MD[1,2,6], Tamas Csipo, MD[1,2], Agnes Lipecz, MD[1,2], Priya Balasubramanian DVM, PhD[1,2,] Eszter Farkas, PhD[6], Peter Toth, MD, PhD [1,2,7], Farzaneh Sorond, MD, PhD[8], Anna Csiszar MD, PhD[1,2,6], Zoltan Ungvari MD, PhD[1,2,6,9]

1) Vascular Cognitive Impairment and Neurodegeneration Program, Reynolds Oklahoma Center on Aging, University of Oklahoma Health Sciences Center, Oklahoma City, OK

2) Translational Geroscience Laboratory, Department of Geriatric Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

3) Heart and Vascular Center, Semmelweis University, Budapest, Hungary

4) Veterans Affairs Medical Center, Oklahoma City, OK

5) Department of Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

6) Vascular Cognitive Impairment Program, Department of Medical Physics and Informatics, University of Szeged, Szeged, Hungary

7) Cerebrovascular Laboratory, Department of Neurosurgery and Szentagothai Research Center, University of Pecs Medical School, Pecs, Hungary

8) Department of Neurology, Northwestern University, Chicago, IL

9) Semmelweis University, Department of Pulmonology, Budapest, Hungary

Abstract

There has been an increasing appreciation of the role of vascular contributions to cognitive impairment and dementia (VCID) associated with old age. Strong preclinical and translational evidence links age-related dysfunction and structural alterations of the cerebral arteries, arterioles and capillaries to the pathogenesis of many types of dementia in the elderly, including Alzheimer's disease. The low pressure, low velocity and large volume venous circulation of the brain also plays critical roles in the maintenance of homeostasis in the central nervous system. Despite its physiological importance the role of age-relate alterations of the brain venous circulation in the pathogenesis of vascular cognitive impairment and dementia is much less understood. This overview discusses the role of cerebral veins in the pathogenesis of VCID. Pathophysiological consequences of age-related dysregulation of the cerebral venous circulation are explored, including blood brain barrier disruption, neuroinflammation, exacerbation of neurodegeneration, development of cerebral microhemorrhages of venous origin, altered production of cerebrospinal fluid, impiared function of the glymphatics system, dysregulation of cerebral blood flow and ischemic neuronal dysfunction and damage. Understanding the age-related functional and phenotypic alterations of the cerebral venous circulation is critical for developing new preventive, diagnostic, and therapeutic approaches to preserve brain health in older individuals.

Key words: vascular contributions to cognitive impairment and dementia (VCID)**,** VCI, senescence, vein, cerebral circulation

1. Introduction

Recent advances in cerebrovascular pathophysiology and vascular aging research highlight the significance of vascular contributions to cognitive impairment and dementia (VCID) associated with old age(79, 176, 189). VCID encompasses all types of vascular pathology-related cognitive decline, the most common being cerebral small vessel disease. Vascular cognitive impairment and dementia are now recognized as the second most common cause of cognitive decline in older individuals often overlapping with Alzheimer's disease. There is increasing recognition that vascular mechanisms contributing to cognitive impairment are potentially reversible and treatments and interventions that preserve cerebrovascular health may help to prevent cognitive decline, even of the Alzheimer type. The prevalence of vascular cognitive impairment and dementia is strongly age-related(63). Accordingly, there is ever growing evidence that age-related structural and functional alterations of large arteries, arterioles and capillaries lead to dysregulation of cerebral blood flow and ischemia, blood brain barrier disruption, impaired clearance of metabolic by-products, increased neuroinflammation and impaired paracrine regulation of the function of neighboring cells (e.g. neuronal stem cells), all of which act synergistically to impair brain function. There is also strong evidence demonstrating the contribution of age-related alterations in arteriolar microvessels and capillaries to Alzheimer's disease(164, 176).

The low pressure, low velocity and large volume venous circulation of the brain plays critical roles in the maintenance of homeostasis in the central nervous system. Despite its physiological importance the role of age-relate alterations of the brain venous circulation in the
pathogenesis of vascular cognitive impairment and dementia and Alzheimer's disease is much less understood. In this review, the effect of aging on the functional and structural integrity of the brain venous circulation is considered in terms of potential mechanisms involved in the pathogenesis of neurodegeneration and cognitive decline.

2. Anatomy and physiology of cerebral venous circulation and cerebrospinal fluid dynamics

The venous circulation of the brain consists of two main systems: the superficial (cortical) and the deep venous system (Figure 1). The superficial venous system drains the cortex and superficial white matter mainly collected by dural sinuses, the superior sagittal sinus and the cavernous sinus. In addition to direct contacts to sinuses, venous blood also reaches the sinuses through bridging veins between the superficial venous network and the superior saggital sinus running in the subdural space. The deep venous system, which consists of the internal cerebral veins, vein of Rosenthal and Galen and their collaterals, drains the deep white matter, the lateral ventricle, third ventricle and basal cistern via the straight sinus. Ultimately the venous blood of the superficial and deep system drains through the sigmoid sinus to the veins of the neck, most importantly to the jugular veins(105, 236). The intracerebral veins possess no valves, and their walls are extremely thin (and vulnerable) due to the absence of a well-developed smooth muscle layer(65, 105).

The internal jugular veins are considered to be the main pathways of cerebral venous drainage. However, angiographic and anatomical evidence demonstrate that a wide anatomical variability exists that results in varying contributions of jugular and non-jugular venous drainage(64). Furthermore, there is significant postural dependency of the cerebral venous outflow(203). In the supine position there is a predominance of the jugular veins in cerebrovenous drainage. In contrast, in the erect position, the vertebral venous system represents a major outflow pathway(203). For example, the inner jugular vein diameter

increases and the distensibility decreases while reclining due to the intraluminal pressure elevation – forming most of the cerebral venous drainage in the majority of normal subjects (about 70%), called jugular drainers. In the remaining 30% of the normal population draining occurs via the vertebral veins, deep neck veins or via the intraspinal venous system. Reduced diameter and high distensibility of the inner jugular vein could be observed in the erect body position when the intraluminal venous pressure is low as blood flow to the atrium is facilitated by gravity and most of the cerebral venous drainage is ensured by the vertebral venous system(27, 64).

To understand brain pathologies of venous origin it is crucial to understand to crosstalk between cerebral blood flow (CBF) and cerebrospinal fluid (CSF) and thus so the interaction between the venous system and the CSF. According to the classical theory, CSF is produced by the choroid plexus and flows through the ventricles, cisterns and subarachnoid space to ultimately be absorbed into the venous blood by the arachnoid villi(19, 33). The pressure gradient needed for this absorption between the two spaces is 5-7 mmHg. Thus, any increase in the venous sinus pressure may significantly affect CSF absorption (22). In addition to the unidirectional flow of CSF from the site of production to the site of absorption, it also exhibits pulsatility(19, 212) as the fluid compartment of CSF serves as a Windkessel, dampening the arterial pulse wave entering the skull. Since the brain requires nonpulsatile and continuous flow, the Windkessel effect is a critical function of both the CSF and cerebral venous fluid compartments. The Monro-Kellie doctrine describes the principle of homeostatic intracerebral volume regulation, which stipulates that the total volume of the parenchyma, cerebrospinal fluid, and blood remains constant. Accordingly, since blood and CSF are not compressible the arterial pulsation results in CSF shift through foramen magnum or a compression of the veins. Thus any change in the venous circulation, namely pressure overload, backward flow, or even a change in the compliance of the neck and brain veins not just affects the drainage of the brain, but may also lead to alterations in CSF homeostasis(19).

3. Structural and functional alterations affecting the cerebral venous circulation in aging

3.1. Structural/morphological alterations and altered distensibility of cerebral veins in aging

Aging is known to alter the structure of cerebral capillaries, promoting structural abnormalities of the basement membrane, increasing perivascular collagen deposits, and leading to basement membrane thickening(69). Age-related increased collagenosis also occurs in cerebral veins and venules(34, 130), due to increased expression and deposition of collagen subtypes I and III in the vascular wall. This age-related remodeling of the venous wall is thought to maintain venous tensile strength in response to pathologic penetration of the increased arterial pulse wave (due to stiffening of large conduit arteries) through the capillary network into the venous system in aging(172). Venous collagenosis was reported to be increased in brains with manifest leukoaraiosis(34), suggesting that pathological remodeling of the venous wall may contribute to white matter lesions both in normal aging and in Alzheimer's disease(104).

Arteriolar tortuosity is a frequent age-related vascular pathology in the white matter, that often associates with leukoaraiosis(34). Tortuous vessels are often surrounded by enlarged perivascular spaces corresponding to 'État criblé' (also known as status cribrosum) (34). Histopathological examination of postmortem brains of older individuals as well as advanced imaging modalities in vivo (e.g. ultra-high field time-of-flight MR angiography and susceptibility-weighted imaging [SWI]) reveal that venules also often exhibit age-related increased tortuosity(100, 148) (Figure 2A). Recent studies provide preliminary evidence that venular tortuosity may be an early neuroimaging marker of small vessel disease and may

correlate with white matter hyperintensities and/or cerebral microhemorrhages(148). A recent study comparing deep medullary veins visualized on 7T-MRI revealed that patients with early Alzheimer's disease also exhibit increased venular tortuosity(32). It should be noted that the existing imaging studies reporting venular tortuosity in aging and/or in Alzheimer's disease patients are cross-sectional in nature, thus its remains to be determined whether venular tortuosity is a progressive condition.

The mechanisms underlying increased venous tortuosity are multifaceted and, based on analog mechanisms manifested in the peripheral circulation, likely include increased cerebral venular pressure (similar to the hemodynamic environment promoting varicose vein formation in the lower extremities(112)), altered elasticity of the vascular wall, degenerative changes of the smooth muscle and endothelial cells and pathological remodeling of the extracellular matrix and basal membrane(100). Age-related mechanisms that promote adverse remodeling of the venular wall include impaired expression of angiogenic and growth factors (e.g. VEGF), cellular senescence, oxidative stress and dysregulation of MMPs(100). Interestingly, pharmacological depletion of mural cells using a platelet-derived growth factor receptor-beta antagonist was reported to increase venular tortuosity in animal models(111), mimicking the aging phenotype. It is likely that cerebral venous tortuosity correlates with the presence of retinal tortuous veins, due to shared etiology(83). In that regard it is interesting that increased tortuosity of retinal venules was shown to predict Alzheimer's disease(39). The critical role for increased venous pressure in the genesis of venous tortuosity is supported by the findings that patients with venous congestion related to an intracranial dural arteriovenous fistula also exhibit tortuous, engorged pial veins clearly visible on angiograms(222). Examples of focal and diffuse tortuosity in cerebral veins due intracranial arteriovenous fistulas are shown in Figure 2B-D.

Age-related alterations of the bridging veins, which connect the superficial venous network to dural sinuses, play a central role in traumatic brain injury-related subdural bleedings in the elderly(84). Because of brain atrophy and subsequent expansion of the subdural space increased mechanical tension is imposed on the bridging veins in the elderly(84, 229). This increased mechanical burden combined with the age-related decline in elasticity of venous wall predispose the bridging veins to rupture in response to even minor brain trauma, resulting in increased incidence of bleedings into the subdural space in older adults(84, 229).

The venous wall is significantly more distensible compared to the arterial wall, which has important physiological relevance. The distensibility of the internal jugular vein is a major determinant of cerebral venous drainage and keeps cerebral venous pressure within normal values. There is strong evidence that aging reduces the distensibility of the upper limb venous system by 38% when determined by plethysmography(75). Aging also decreases jugular vein distensibility by 68% (measured by ultrasonography) in the supine position (although this effect may have postural dependency(27)). It is likely that due to an age-related reduction in distensibility, the inner jugular vein loses its compensatory ability to increased transmural pressure and thereby predisposes the cerebral venous system to venous hypertension. It is likely that the effects of aging on the venous wall biomechanics are multifaceted and include age-related pathological remodelling of the venous wall, including changes in the extracellular matrix and the medial layer. Age-related changes of the biomechanical properties of jugular venous walls are also defined by aging-induced changes in venous tone, intra- and extraluminal pressure, and the relationship to surrounding tissues. The age-related changes in the multilevel control of venous biomechanics likely includes alterations in intrinsic local myogenic and humoral mechanisms as well as extrinsic systemic hormonal and nervous influences(129). Hemodynamic factors (changes in pressure and flow)

together with inflammatory processes contribute to the age-related changes in the biomechanical properties of the jugular veins, which further promote age-related progression of venous dysfunction(127). Several age-associated pathological conditions, including chronic heart failure, pulmonary hypertension and chronic obstructive pulmonary disease can elevate central venous pressure in the elderly and thereby alter biomechanical properties of the veins. In addition, sex, obesity and sedentary lifestyle may importantly modulate the effects of aging on biomechanical properties of the cerebral venous system(8, 9, 121), similar to peripheral veins(71, 119). Studies on 70 adult Caucasian twins from the Italian twin registry demonstrate that hereditary factors are responsible for 30-70% of the biomechanical properties of internal jugular veins(170). Longitudinal studies should elucidate how genetic factors determine successful venous aging and predispose to exacerbated pathological remodelling of the cerebral venous system in aging.

Numerous malformations can also affect the venous circulation of the neck in older subjects, leading to impaired venous drainage in the brain(236). Causes of narrowing or occlusion can be intraluminar, such as septa, flaps, abnormal valves or extraluminar such as any anatomical or pathological mass compressing the vessel.

Abnormal remodeling and increased stiffness of the venous wall and/or increases in venous pressure may impair the Windkessel effect of the venous circulation(19, 212). As the venous circulation plays a bigger role in the Windkessel effect and dampening of arterial pulsatility with aging, any age-related alteration that affects the venous system will exert a significant impact on penetration of the arterial pressure wave into the brain(19). Increased pulse pressure can reach the venous side through the arterial tree due to the lack of proper myogenic autoregulatory protection in the proximal cerebral resistance arteries(174, 176, 178). In addition, increased arterial pulsation can be transmitted to venous pulsation indirectly through the CSF. In the presence of age-related alterations of CSF circulation, when compliance of the CSF compartment is decreased, less dampened pulse waves can reach the venules and veins. The age-related increased pulse pressure due to arterial stiffening and the lack of arterial myogenic protection together with the decreased Windkessel function of the CSF compartment imposes mechanical stress on the venous wall in aged individuals. There is also a cross talk between the different types of venous abnormalities as structural and morphological changes may lead to hemodynamic consequences. For example pressure elevation in the sagittal sinus will also increase pressure in the cortical veins making them more stiff and resistant against compression, compromising the Windkessel effect(19).

Previous preclinical studies have characterized age-related degenerative changes and pathological remodeling in venous valves(87), which likely contribute to venous valve insufficiency associated with old age. Clinical studies confirm that aging is associated with pathological remodeling of venous valves in the peripheral venous circulation, which likely impairs valve function(146, 205). Based on our understanding of the pathogenesis of chronic venous insufficiency in the peripheral circulation, it is likely that age-related changes in cerebral venous valves contribute to valvular incompetence(204), leading to venous reflux and cerebral venous hypertension.

3.2. Jugular venous reflux and increased cerebral venous pressure

Increased cerebral venous pressure is likely to contribute to pathological processes that play a significant role in development of brain pathologies in older individuals, including microhemorrhages, blood-brain-barrier disruption and perivascular inflammation(125, 191). When venous hypertension occurs in the superior sagittal sinus, CSF absorption is also impaired, leading to altered CSF outflow. Factors that contribute to increased cerebral venous pressure include penetration of arterial hypertension to the venous circulation, venous

drainage impairment, presence of an arteriovenous fistula and retrograde transmission of increased central venous pressure to the cerebral venous circulation.

Jugular venous reflux is a clinically potentially important hemodynamic abnormality (Figure 3). It can be caused for example by physiologic compression of the brachiocephalic vein that leads to stagnation or reversal of the internal jugular vein flow, promoting increased cerebral venous pressure. The pressure gradient determines the flow in the veins and a missing or damaged internal jugular vein valve can easily lead to retrograde flow(45).

The internal jugular vein valve, which is the only venous valve situated in the venous circulation between the heart and the brain, is critical for the prevention of retrograde flow of venous blood. Despite their clinical significance, the presence and function of the valves in the internal jugular veins are often overlooked(62, 115). Anatomical evidence obtained in human cadavers suggest that internal jugular vein valve is frequently incompetent. With an incompetent internal jugular vein valve any increase in intrathoracic pressure (e.g. during Valsalva maneuver) could result in jugular venous reflux(236). The incidence of jugular venous reflux has been reported to increase with age(92, 96, 103, 106, 109, 184), likely due to age-related degenerative changes in the venous valves. Interestingly, there are studies extant reporting that incidence of jugular valve incompetence can reach ~30 to 90% in the general population(2, 204). Jugular valve insufficiency and the resulting retrograde jugular venous flow and back transmission of central venous pressure likely contribute to various brain pathologies. Jugular venous reflux was shown to associate with intracranial structural changes in patients with mild cognitive impairment and Alzheimer's disease(21, 24). It has been suggested that jugular venous reflux retrogradely transmits increased venous pressure into the brain, promoting edema as well as a wide range of microvascular pathologies associated with increased venular pressure. There are case reports extant showing that age-related jugular valve incompetence in association with the physical exertion during sexual intercourse possibly can lead to intra-cerebral hemorrhage of venous origin(4).

There are case reports extant suggesting that during central venous catheter placement venous valves located in the right internal jugular vein may be damaged(72, 225). Because the internal jugular valve is often located in the retroclavicular space, the ultrasound assessment of this valve can be difficult. Valve cusps are thin structures and forceful attempts to force a catheter through them may result in valve damage.

3.2. Age-related phenotypic and genotypic changes in endothelial cells

Despite their common developmental origins, endothelial cells in the arterial and venous circulatory system are not identical(61). Functionally, one of the key roles of arteriolar endothelial cells is the regulation of vascular tone and thereby blood flow and the production of a number of trophic factors, paracrine mediators and gaseotransmitters. On the other hand post-capillary venular endothelial cells are the primary site of leukocyte trafficking and stem cell extravasation. Interestingly, recent studies report that cerebral arteries and veins differentially exhibit an endothelial glycocalyx (e.g. in mice cerebral arteries and capillaries have an intact endothelial glycocalyx, but veins and venules do not(231)), which may have relevance for regulation of inflammatory processes. Among the endothelial glycocalyx constituents, syndecan-1 is a main component and it is also predominantly expressed in arterial endothelial cells as compared to venous endothelial cells in the brain(86). Despite the pathophysiological importance of the venous endothelium, the role of age-related functional changes in the venous endothelial cells have not been explored.

There is ample evidence that aging is associated with critical phenotypic alterations in the endothelial cells in the arterial circulation due to age-related changes in their gene expression profile(16, 52, 56, 58, 167, 183, 188, 192, 193, 197). Studies on endothelial cells from diverse vascular beds suggest that aging promotes pro-inflammatory, pro-oxidative and

pro-senescence changes in endothelial gene expression in the arterial circulation altering the cytokine and chemokine secretory profile of endothelial cells(51, 57, 58, 73), dysregulating mitochondrial biogenesis(197), altering transport, barrier and vasomotor function and free radical production(56, 167, 178, 182), impairing angiogenic capacity(16, 51, 192, 193) and facilitating endothelial-leukocyte interactions(51, 53, 185, 198). It can be hypothesized that if aging is associated with gene expression changes in endothelial cells in the venous circulation which are similar to those in endothelial cells in the arterial circulation then these changes may significantly contribute to pathological processes promoting neuroinflammation and impaired tissue homeostasis. Venous endothelial cells express unique molecular markers(86), including Endomucin (*Emcn*)(232), Ephrin type-B receptor 4 (*EphB4)*, Lefty-1, Lefty-2, Neuropilin-2, and *Flt4(61)*. Preliminary analysis did not reveal significant age-related changes in the gene expression profile of these markers in the mouse brain. Further studies are warranted to isolate endothelial cells from the venous circulation based on these surface markers and analyze age-related changes in functionally relevant genes (e.g. inflammation-related gene expression, including adhesion molecules and chemokines). A recent breakthrough study published a single-cell RNA sequencing dataset that defines arterial, capillary and venous endothelial cells in mouse brain(86). This study identified >180 genes that are enriched (over 2 fold) in venous endothelial cells versus capillary endothelial cells (including *Gm5127, Wnt5a, Ptgs2, Cfb, Cfh*). Interestingly, among them *Vcam1* and *Icam1* shows a ~54 fold and ~4 fold enrichment, respectively, in venous endothelial cells versus capillary endothelial cells, which corresponds to the primary role of the post-capillary venules in leukocyte transmigration. Using single-cell RNA sequencing future studies should compare age-related changes in these subsets of endothelial cells.

4. Potential role of pathological alterations of the cerebral venous circulation in neurodegenerative diseases and cognitive decline

The links among alterations in the cerebral venous circulation, neurogenerative diseases and cognitive impairment are not well understood. Here we provide a review of existing data supporting a potentially important role for venous dysfunction in different brain pathological conditions. Some speculations are also offered as to the mechanisms by which alterations of the cerebral venous circulation may contribute to the pathogenesis of age-related cerebral diseases and cognitive decline.

4.1. Chronic cerebrospinal venous insufficiency: lessons from studies on multiple sclerosis

Originally Zamboni et al proposed the hypothesis that cerebrospinal venous insufficiency, caused by intraluminal stenotic malformations in the internal jugular and azygos veins with insufficient opening of collaterals. leads to impaired venous drainage of the brain and thereby contributes to the pathogenesis of multiple sclerosis (MS) (234). This hypothesis was built on the findings of early studies that MS lesions have venous involvement(59, 139, 140). According to Zamboni's hypothesis, cerebrospinal venous insufficiency is similar to chronic venous disorders of the lower extremity in that the altered hemodynamic environment in the venous circulation promotes chronic inflammation, iron deposition and tissue injury(233). In support of this hypothesis Zamboni and co-workers reported that in MS patients there are alterations in venous drainage of the brain(234). However, these results proved to be controversial due to the lack of scientific rigor (e.g. proper controls)(135) and could not be reproduced by other investigators(47, 142, 180), mainly due to the high degree of variability and non-specificity of the diagnostic ultrasound criteria (reflux, internal jugular vein stenosis, absent flow detectable by Doppler ultrasonography in the internal jugular or vertebral veins, reversed postural flow in the internal jugular vein) that define cerebrospinal venous insufficiency. Other investigators

proposed that pulse wave encephalopathy may be an initiating step in the pathogenesis of MS(101). In support of this hypothesis increases in the Virchow-Robin space, decreased intracranial compliance and higher microvascular pulsatility have been reported in MS patients(101). Given the critical role of the venous circulation in inflammatory processes (e.g. endothelium-leukocyte interactions), control of the blood brain barrier, microglia activation and microvascular injury, further studies are warranted to better elucidate the role of hemodynamic factors in general and the venous pathologies in particular in the pathogenesis of various forms of neurodegenerative diseases.

4.2 Leukoaraiosis/white matter hyperintensities

Leukoaraiosis is a radiological finding showing damage in the white matter regions of the brain near the lateral ventricles on CT scans (showing up as hypodense periventricular white-matter lesions) or on T2/FLAIR MRI sequences (white matter hyperintensities or WMHs; Figure 4A). Its clinical significance stems from the association of leukoaraiosis with vascular dementia, gait disturbances and stroke(133). WMHs have been detected in patients with Alzheimer's disease(94, 102, 124) or at risk for developing Alzheimer's disease(46). The current view is that WMHs are early and independent predictors of Alzheimer's disease(131). WMH burden is even more significant in patients with vascular cognitive impairment (6, 30). There are numerous studies attempting to define the neuropathological correlates of WMHs (reviewed recently in reference(100)), which include a variety of small vessel pathologies (accentuation of perivascular Virchow-Robin spaces, sclerotic vessels, microvascular amyloidosis, arteriolosclerosis, hyalinosis and collagenosis), gliosis, periventricular necrosis and axonal degeneration and reactive astrocytosis. Global WMHs are hypoperfused compared with normal white matter, suggesting that ischemia may play a role in their pathogenesis (124).

Important for the present overview is the observation that leukoaraiosis is associated with a number of venous abnormalities, including periventricular venous collagenosis(130) and venular tortuosity. Jugular venous reflux and increased cerebral venous pressure were suggested to contribute to the pathogenesis of leukoaraisosis (44). Chronic cerebral venous hypertension likely decreases cerebral blood flow promoting local ischemia in the white matter(44), disrupts the blood brain barrier promoting perivascular inflammation and exacerbates pathological remodeling of the cerebral venules. Progressive injury of the ischemic periventricular white matter is likely exacerbated by damage to the blood-brain barrier, accumulation of toxic metabolites and pro-inflammatory plasma constituents, the heightened inflammatory status of microglia and astrocytes and/or by the presence of amyloid deposits(102). Higher venous pressure, remodeling of the veins and/or jugular venous reflux may lead to impaired Windkessel effect and increased pulsatility in the capillary bed. Higher pulsatility per se may contribute to the pathogenesis of leukoaraiosis(18).

4.3 Normal pressure hydrocephalus (NPH)

NPH results from an abnormal accumulation of CSF in the ventricles of the brain, leading to ventriculomegaly(67). The enlarged ventricles exert increased pressure on the adjacent cortical tissue, impairing brain function and resulting in gait disturbance, dementia, and urinary incontinence(67). NPH patients are known to have an accumulation of CSF and dilation of the ventricles without an intracranial pressure elevation, which is canonically explained by lower absorption of CSF by the arachnoid villi to the venous circulation(152). An alternative hypothesis focuses on the decreased venous compliance in NPH patients(17). In NPH patients intracranial venous flow and pressure are abnormal(110) and it is believed that an elevation of venous pressure contributes significantly to the neuronal damage and dysfunction associated with NPH(17). Venous hypertension may not only promote pulse

wave encephalopathy but also impair reabsorption of CSF through the arachnoid villi leading to abnormal accumulation of CSF(152). Interestingly, there is a higher prevalence of cardiovascular diseases in patients with NPH, suggesting that the pathogenesis of NPH and cardiovascular disease may be linked(66), for example by increasing jugular venous pressure.

4.4 Role of the venous circulation in the pathogenesis of cerebral microhemorrhages

Cerebral microhemorrhages (CMHs, also known as "cerebral microbleeds")(191), which are associated with rupture of small intracerebral vessels, are highly prevalent in patients 65 and older(191). CMHs have been defined as multiple small (<5 to 10 mm in diameter) round or oval hypointense lesions on T2*-weighted Gradient-Recall Echo (T2*-GRE) MRI sequences, which correspond to focal, persisting hemosiderin depositions in microglia. There is strong evidence from population-based cross-sectional studies that CMHs contribute significantly to cognitive decline(37, 89, 138, 191, 206, 219, 220, 224, 227, 228).

Although many CMHs likely originate from small arterioles (they main risk factors being aging, hypertension and amyloid deposition), there is increasing evidence that rupture of small veins and venules as well as capillaries can also result in CMHs(161, 191). In support if this concept recent evidence shows that development of CMHs can be causally linked to the performance of Valsalva maneuvers(195). The Valsalva maneuver (defined as a forced expiratory blow against a closed glottis) is common in many everyday activities that involve moderate exertion, including weight lifting, blowing air into inflatable devices or musical instruments (e.g. playing the oboe), intense coughing, vomiting, nose blowing and strain during defecation or sexual intercourse(195). Intrathoracic pressure in these conditions may increase well over >150-200 mmHg(149), which is transmitted to the venous circulation, resulting in a substantial elevation in central venous pressure(226). If in older individuals the internal jugular vein valves are incompetent, they would enable retrograde transmission of increased venous pressure to the cerebral venous system during the Valsalva maneuver(42, 70, 235, 236). It is likely that when in elderly patients venous pressure exceeds the threshold for structural injury in thin-walled cerebral venules, multifocal venous CMHs ensue. In support of this concept, there is direct evidence that retinal hemorrhages of venous origin can be also generated by Valsalva maneuvers(3, 38). Preclinical studies on mouse models with surgical jugular vein occlusion(14) confirm that elevation of venous pressure in the cerebral circulation promotes the development of CMHs (Fulop and Ungvari, 2018, unpublished observation). Further, when retrograde penetration of a venous pressure wave into the cerebral venous circulation is mimicked experimentally by injecting a carmine-gelatine solution under high pressure into the vein of Galen in human cadavers, multifocal venous ruptures develop. These studies suggest that pressure-induced venous ruptures are predominantly localized to the region of lateral ventricle, where there are connections between medullary and subependymal veins(147). It is likely that these vessels are more prone to rupture due to their branching pattern, anatomy as well as the structural characteristics of their walls.

Another line of evidence supporting an important role of venous aging in the pathogenesis of intracerebral hemorrhages comes from studies on arteriovenous malformations (AVM)(134). AVMs are congenital vascular lesions (incidence: ~ 1 per 100,000 persons). The risk for AVM rupture significantly increases with age(50, 107), suggesting that with advanced aging the fragility of the venous wall increases. We posit that age-related structural changes in the venular wall also promote venular fragility, contributing to the pathogenesis of CMHs of venous origin in older individuals.

4.5. Role of the venous circulation in the pathogenesis of cerebral microinfarcts

Cerebral microinfarcts are small (0.05–3 mm in diameter) ischemic lesions that are prevalent in the aged human brain(10, 11, 35, 85). The association between the number of

cerebral microinfarcts and cognitive decline has been established by population-based radiological and pathological studies and confirmed by histopathological examinations(77, 154, 155, 209, 210). Current thinking suggests that cerebral microinfarcts develop due to critical ischemia induced by the occlusion of arteriolar microvessels, which supply the respective small volume of brain tissue. Recent experimental studies demonstrated the occlusion of small venules can also lead to the genesis of cerebral microinfarcts, which appear identical to those resulting from arteriole occlusion(85). On the basis of these observations it has been proposed that cerebral venule pathology may also contribute to the pathogenesis of cerebral microinfarcts in older adults(85). Future clinical and experimental studies are warranted to establish the association between microinfarcts and venular pathology.

4.6. Glymphatic circulation

The brain parenchyma does not contain lymphatic vessels. Instead, in the central nervous system the 'glymphatic' system (paravascular system) functions as a waste clearance pathway(98). The glymphatic system consists of a para-arterial influx route for cerebrospinal fluid to enter the brain parenchyma through the Virchow-Robin space and a para-venous efflux route. The inner wall of the perivascular space containing the flowing paravascular fluid is the outer wall of the vessels, and the outer wall of perivascular space is covered by astrocytic endfeet. According to the currently accepted hypothesis circulation of the cerebrospinal fluid in the paravascular system and the exchange of solutes between cerebrospinal fluid and interstitial fluid is driven primarily by arterial pulsation(29). Clearance of soluble proteins and metabolic by-products from the brain parenchyma is accomplished through convective bulk flow of interstitial fluid, facilitated by aquaporin 4 channels located on the astrocytic end-feet(26) (although there are important theoretical and experimental studies extant questioning the exact role of these mechanisms(99, 153)). There is experimental evidence that amyloid beta injected directly to the brain parenchyma is cleared through the glymphatic system along the large veins(91). It is believed that the glymphatic system drains into lymphatic vessels in the meninges (123). It can be speculated that altered cerebral venous circulation may affect this clearance mechanism indirectly in older individuals. Since the interstitial fluid – cerebrospinal fluid mixture is partly collected through the arachnoid villi, the elevated venous pressure could adversely impact its reabsorption.

4.7 Cognitive dysfunction in heart failure

Chronic heart failure is a significant health problem in the Western world that affects ≥ 10% of persons 70 years of age or older(116). Cognitive impairment is an important complication of heart failure among elderly people(20, 90, 223), with an incidence ranging from 25% to 80%)(116). Heart failure exerts multifaceted effects on the cerebral circulation(97). On the one hand, it attenuates cerebral blood flow by decreasing cardiac output (forward failure)(41, 48, 82, 122, 145), lowering blood pressure and impairing cerebrovascular reactivity, all of which have direct negative effects on brain function. Cerebrovascular autoregulation, which maintains cerebral blood flow constant despite changes in blood pressure in healthy subjects, is abnormal in heart failure patients, predisposing these patients to ischemic neuronal injury(36, 76). On the other hand, heart failure also causes systemic venous congestion (backward failure), which associates with increased jugular venous pressure and possibly reflux(218). There is evidence suggesting that heart failure patients exhibit WMHs(5), supporting the hypothesis that increased cerebral venous pressure is causally linked to the pathogenesis of leukoaraiosis (Figure 4A and B). Backward failure also likely leads to higher capillary pulsatility and decreased waste clearance through the perivascular glymphatic system.

5. Perspectives

Although in the past two decades significant progress has been achieved in understanding age-related alterations in vascular function and phenotype in the arterial circulation, research efforts should persist in this direction to investigate similar alterations in the venous circulation. New investigations are needed to elucidate the mechanism by which age-related alterations in the venous circulation may lead to blood brain barrier disruption, neuroinflammation, dysregulation of CBF and local ischemia, promoting white matter injury and exacerbating VCI. Understanding the interaction of processes of aging and chronic diseases (e.g. hypertension, metabolic diseases) in the context of venous pathologies contributing to VCI should be a high priority. Studies on the venous circulation in both animal models of aging and accelerated vascular aging are warranted(162, 164). In addition, animal models to study the pathophysiological roles of increased cerebral venous pressure are needed. Potentially useful models include the mouse model proposed by Auletta et al., which involves surgical occlusion of the jugular veins in mice (14). The authors have characterized the model, which can be adapted to study consequences of cerebral venous hypertension as they relate to BBB disruption, dysregulation of CBF, white matter hyperintensities, pathogenesis of cerebral microhemorrhages of venous origin, cognitive impairment and gait disturbances. Further, better alignment of preclinical studies on venous aging and human investigations is needed.

Critical areas of research, based on recent achievements in the biology of aging, should focus on the role of known cellular and molecular mechanisms of aging in pathological alterations of the venous circulation. New studies investigating role of sterile(221) and pathogen-induced vascular inflammation in the venous circulation are warranted. Importantly, in the United States over 90% of adults 80 years of age or older have persistent human cytomegalovirus (CMV) infection(1, 93, 114, 132, 157, 160). CMV replicates in the vascular endothelial cells, including venous endothelial cells, during the entire life of the host following initial infection. Severity of CMV infection (assessed on the basis of circulating antibody titers) was shown to predict increased incidence of frailty and risk of mortality in older adults(214). There is also evidence linking CMV infection to sinus vein thrombosis(150). Additional studies invetsigating the pathogenic role of CMV-induced alterations in venous endothelial cells as they relate to heightened inflammatory status, structural remodeling, microhemorrhages and Alzheimer's pathology are needed. Additional important areas of research should focus on age-related changes in extracellular matrix(126, 187, 194, 200), oxidative stress(56, 60, 108, 167, 187), mechanisms involved in altered cellular stress resilience(108, 166, 185, 186, 196, 202), pathways involved in cellular senescence(40, 136, 144, 177, 190, 213, 230), the pathogenic role of the renin-angiotensin system(55, 159, 181, 215-217), altered nutrient sensing pathways(7, 113, 173, 201), epigenetic factors(80, 199) and neuroendocrine mechanisms of aging(12, 13, 25, 68, 137, 141, 171, 211), including IGF-1 deficiency(15, 74, 156, 163, 165, 168, 175, 179). Recent studies(118, 158) identified mTOR as a critical factor contributing to cerebral vascular damage and dysfunction in Alzheimer's disease models(117, 118, 207, 208) and in models of VCI(95). It has to be determined how the pharmacological targeting of this pathway may affect the cerebral venous circulation. Innovative strategies need to be developed to improve the health of the venous circulation, including novel pharmacological strategies(28, 53, 54, 118, 143, 158, 167) and modification of lifestyle and dietary factors(78, 81, 88, 128, 211).

To better understand the relationships between functional alterations of venous circulation, prospective clinical studies, similar to the Heart-Brain Study in the Netherlands(90), are needed. The Heart-Brain Study investigates the link between the hemodynamic status of the heart and the brain, and cognitive impairment in heart failure patients. Specifically, the Heart-Brain Study hypothesizes that the impaired hemodynamic

status of the heart and the consequential brain hypoperfusion are important determinants of VCI. Because backward failure and alterations of the venous circulation likely affect the brain, if would be advantageous to also include in the study design endpoints that reflect jugular venous reflux and cerebral venous pressure/microvascular damage. Using additional sensitive assays to detect markers of neuroinflammation(151) and behavioral consequences(23, 31, 120, 169, 211) would benefit both clinical and preclinical studies as well.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

This work was supported by grants from the American Heart Association (ST), the Oklahoma Center for the Advancement of Science and Technology (to AC, AY, ZU), the National Institute on Aging ((R01-AG055395, R01-AG047879; R01-AG038747), the National Institute of Neurological Disorders and Stroke (NINDS; R01-NS100782, R01-NS056218), the Department of Veterans Affairs (Merit Number 1I01CX000340), a Pilot Grant from the Stephenson Cancer Center funded by the National Cancer Institute Cancer Center Support Grant P30CA225520 awarded to the University of Oklahoma Stephenson Cancer Center, the Oklahoma Shared Clinical and Translational Resources (OSCTR) program funded by the National Institute of General Medical Sciences (U54GM104938, to AY), the Presbyterian Health Foundation (to ZU, AC, AY, CP), the European Union-funded grants EFOP-3.6.1-16-2016-00008, 20765-3/2018/FEKUTSTRAT, EFOP-3.6.2.-16-2017-00008, GINOP-2.3.2-15-2016-00048 and GINOP-2.3.3-15-2016-00032; the National Research, Development and Innovation Office (NKFI-FK123798), the Hungarian Academy of Sciences (Bolyai Research Scholarship BO/00634/15) and the ÚNKP-18-4-PTE-6 New National Excellence Program of the Ministry of Human Capacities (to PT). The authors acknowledge the support from the NIA-funded Geroscience Training Program in Oklahoma (T32AG052363). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure legends

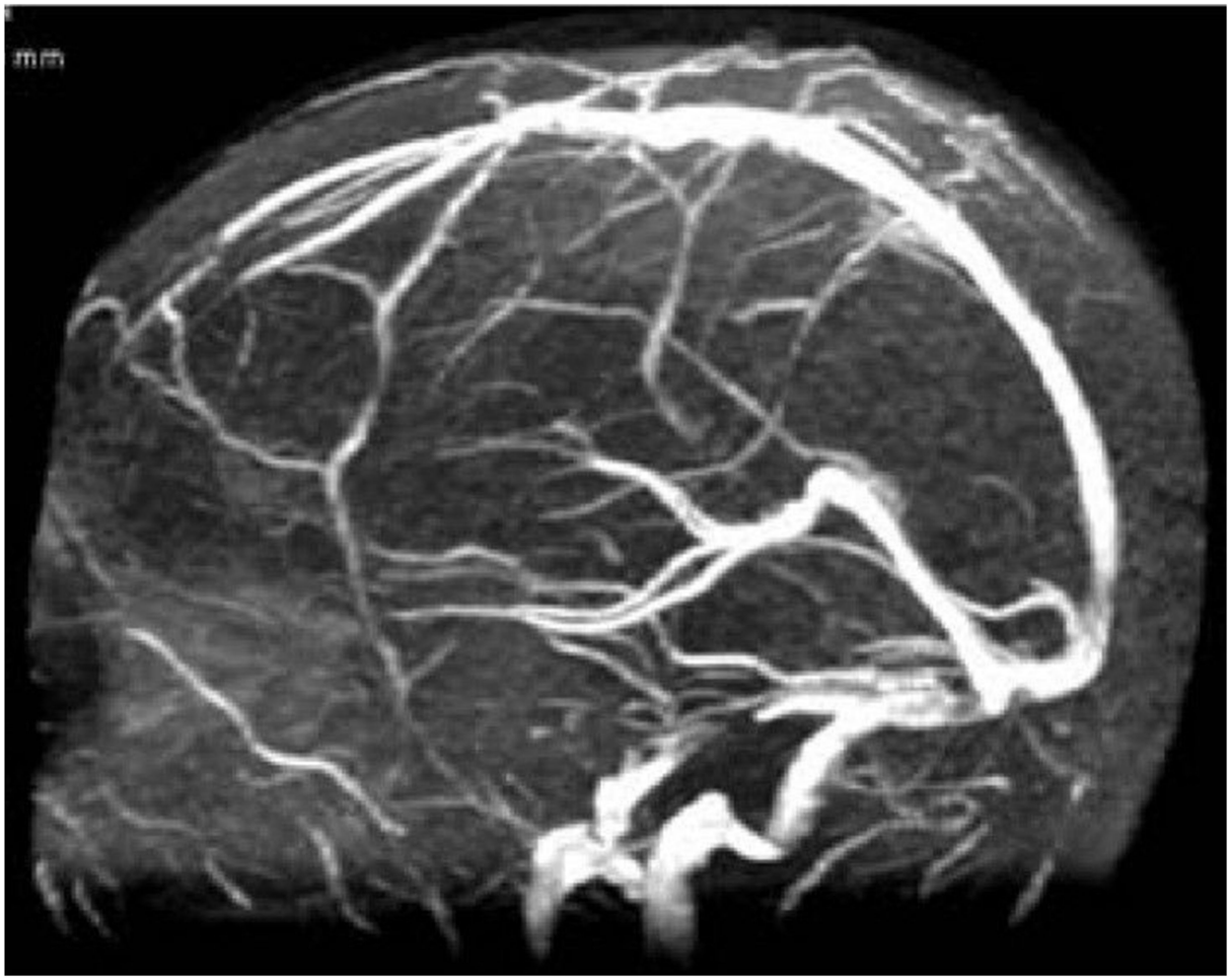
Figure 1. Venous drainage of the central nervous system. Panel A: Venous phase cerebral angiogram showing most of the cerebral venous structures. Image is taken from Coutinho et al. (49). Panel B: Normal anatomy of the cerebral venous system

Figure 2. Cerebral venous tortuosity – a potential radiological sign of increased venous pressure. Panel A) Detection of tortuosity in small intracerebral venules on susceptibility-weighted image (SWI; the MRI image was taken without the use of any contrast agents at 7T). "b" indicates a tortuous venule, whereas "c" marks a straight venule. "a" is an example of a venule that would not be included in the statistical evaluation of venous tortuosity because it was traced by only 1 of the 3 raters. Image is taken from reference(148). B-D) Examples of focal (B) and diffuse (C) tortuosity in cortical veins on lateral views of the venous phase of cerebral angiograms in patients with venous congestion related to intracranial arteriovenous fistulas. Panel D: Frontal projection from cerebral angiogram showing venous tortuosity due to a dural arteriovenous fistula. Images were kindly provided by Dr. Ali Shaibani (Department of Neuroradiology, Northwestern University).

Figure 3. **Pathophysiology of jugular venous reflux**. Panel A: Retrograde flow detected by color duplex and in the Doppler spectrum during Valsalva maneuver (VM) reveals jugular venous reflux in an older individual (mean age of study participants: 74±12 years). Image was taken from reference(43). Panel B: Scheme depicting the role of jugular venous reflux in transmission of increased central venous pressure to the cerebral veins and its consequences in older adults. Jugular venous reflux occurs when increased intrathoracic pressure elevates central venous pressure and the resulting venous pressure wave is beyond the competence of internal jugular venous valves. Valsalva maneuver-induced jugular venous reflux may retrogradely transmit venous hypertension into cerebral venous system, decreasing cerebral perfusion pressure and consequently reducing cerebral blood flow and causing damage to the thin-walled venules, including cerebral microhemorrhages of venous origin and blood-brain barrier disruption.

Figure 4. Potential contribution of elevated venous pressure to increased incidence of white matter hyperintensities in elderly heart failure patients. In older adults heart failure was shown to associate with WMHs. Panel A: To illustrate this point this MRI scan shows extensive periventricular WMHs on FLAIR sequences in a 64-year-old man with heart failure associated with mild cognitive impairment (FLAIR: fluid-attenuated inversion recovery). Panel B: Scheme depicting putative synergistic effects of heart failure-induced chronic hypoperfusion of the brain and increased venous pressure, which may exacerbate white matter injury promoting cognitive impairment in elderly patients with heart failure. RAAS: renin-angiotensin-aldosterone system

A



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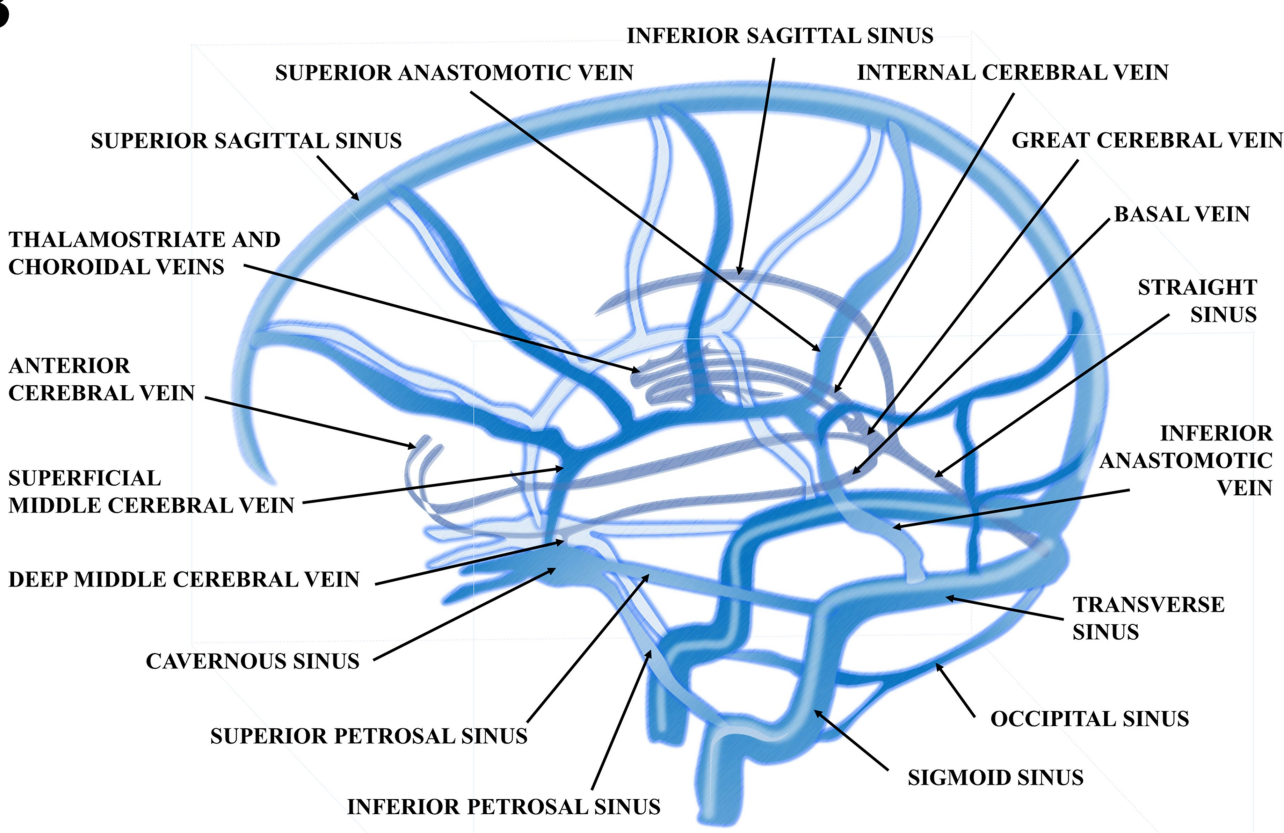

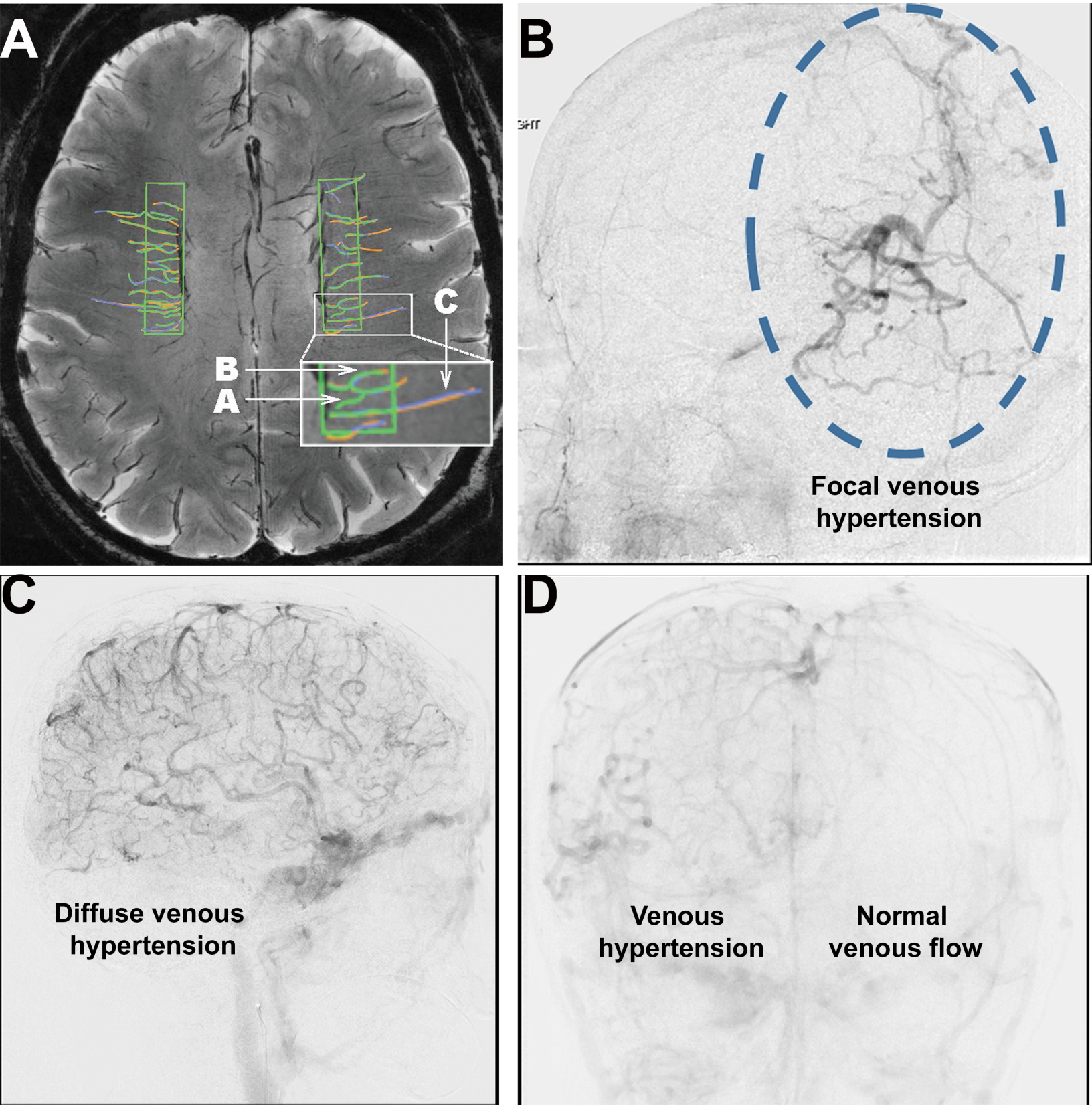

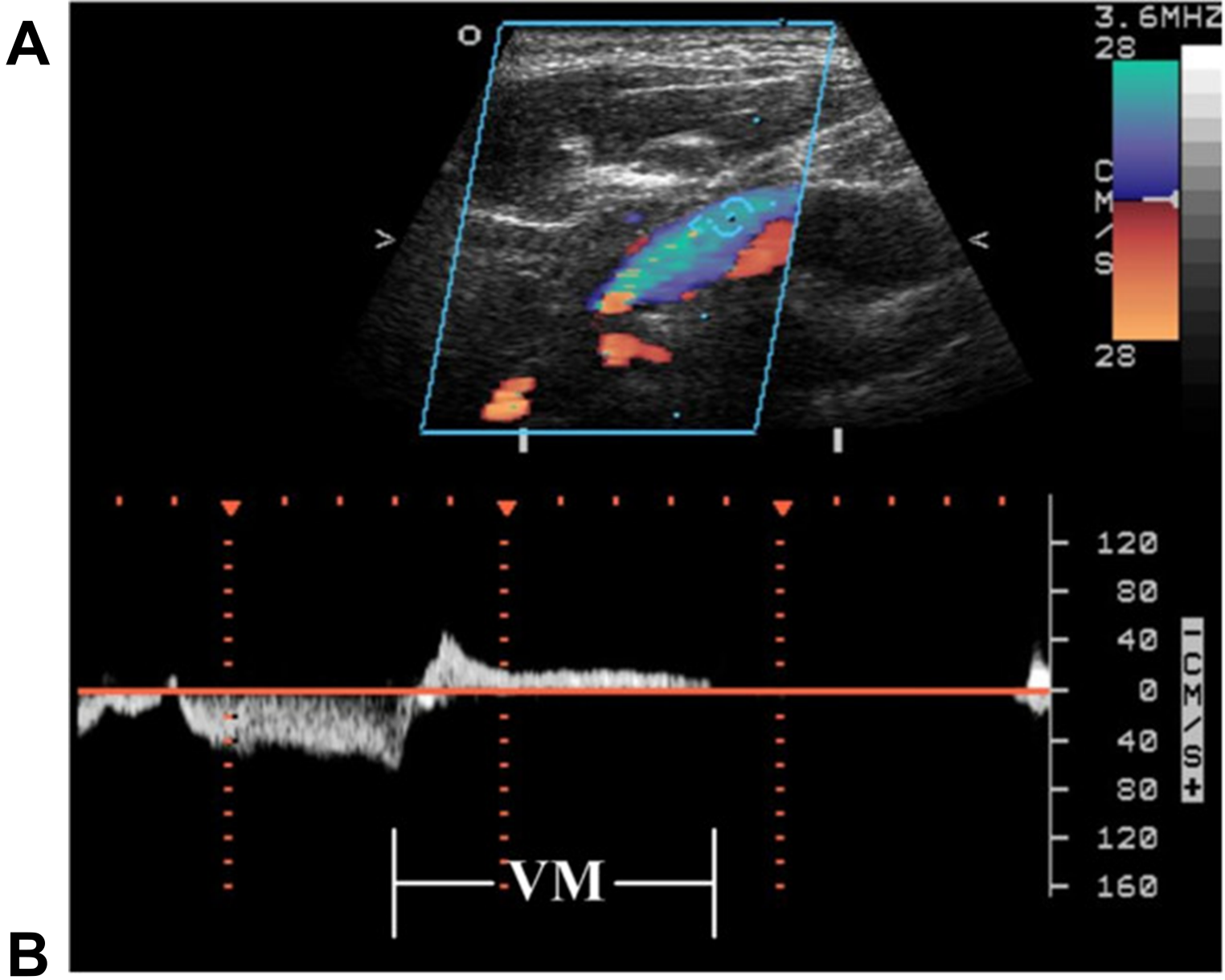

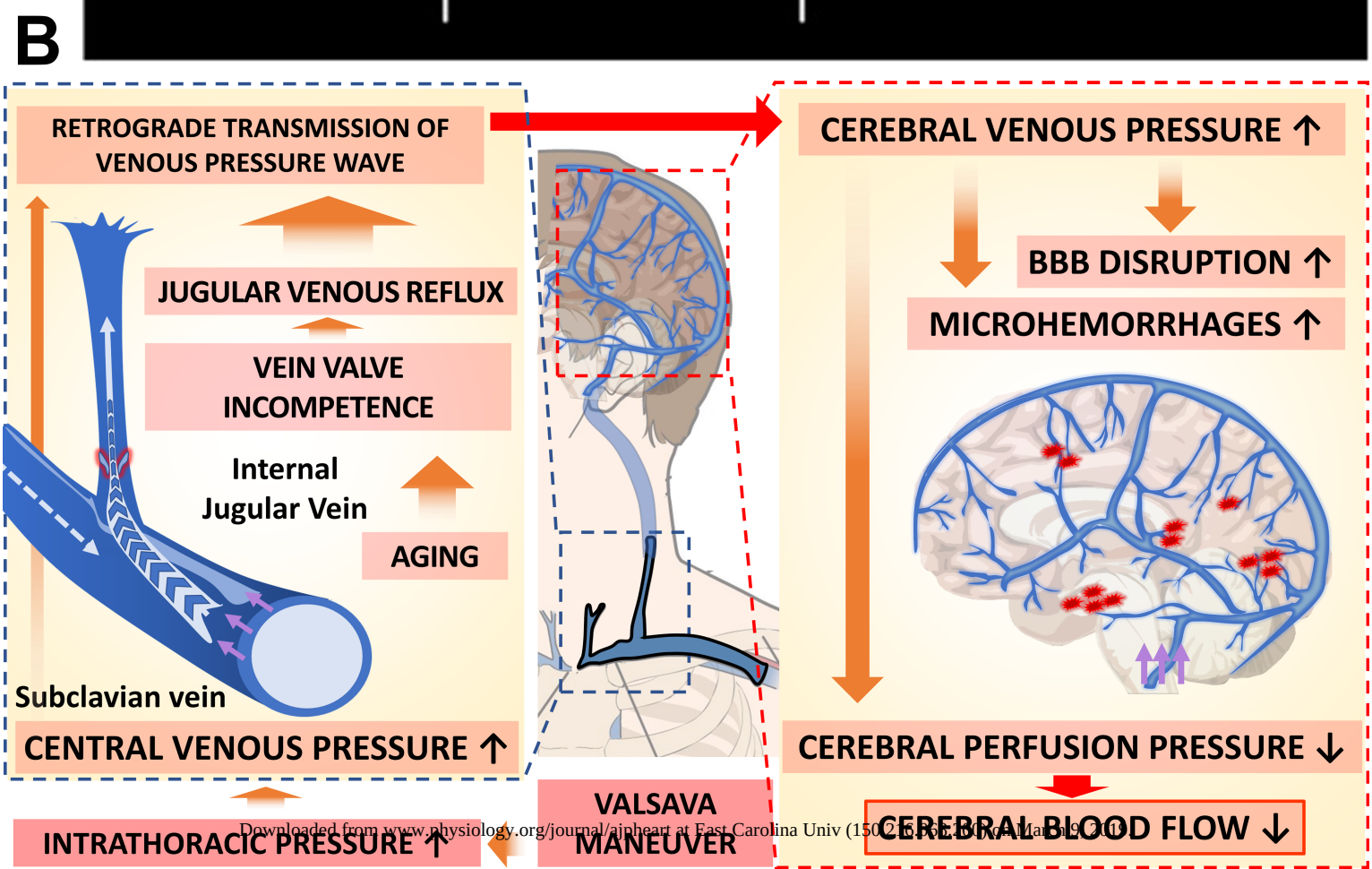

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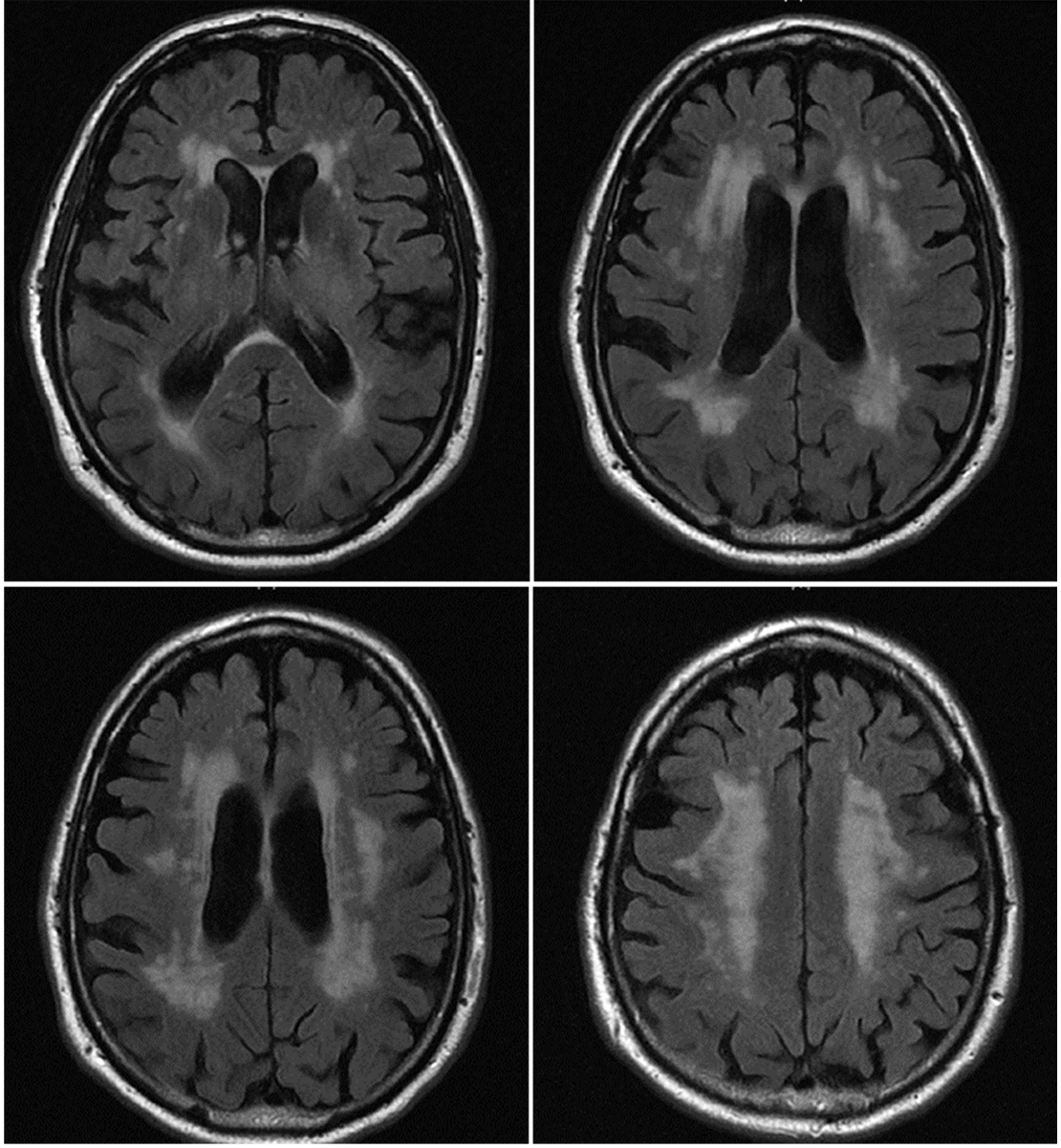

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